

## **REMARKS/ARGUMENTS**

Claims 1-5, 7, 10, 15, 16, 19, 20, and 23-34 remain pending.

## **THE AMENDMENTS**

The amendments to claims 1 and 26 are intended only to further clarify the intended meaning and scope of the claimed invention. These amendments are not intended in any manner, or for any reason, to narrow the scope of any of the claims or of any of the terms of the claims.

## **THE REJECTION**

### **Claims 1-5, 7, 10, 15, 16, 19, 20, and 23-34 Are Rejected Under 35 U.S.C. § 103(a)**

The rejection of all claims as obvious over Timpe U.S. Patent No. 6,063,404 is maintained. The Examiner notes that

Applicant does not specify a particular polymer combination, but rather just merely recites a composition comprising 1) a bioadhesive, water-insoluble, water-swellable cross-linked polycarboxylic polymer and 2) a water-soluble polymer. The claim mentions no particular polymer combination (amounts/ratios). Timpe reads on the invention since Timpe also suggests a combination of the same polymers. See column 3 lines 3-9, 37-43. In the absence of unexpected results, one having ordinary skill in the art would have expected the prior art composition to have extended release properties and the ability to progressively hydrate.

Applicants respectfully disagree. In context, Timpe's disclosure does not support the assertions and conclusions of the Office Action.

As discussed at length in previous Amendments and Responses of record, Timpe's disclosure, focus, and intent all belie any expectation that Timpe's product would provide progressive hydration, and extended release, of a treating agent. Both Timpe's formulation and method of preparing the formulation would not be expected by one of ordinary skill in the art to yield anything that resembles or provides the present invention. Instead, Timpe

should be recognized to teach away from the instant invention, to the extent it is deemed relevant at all to patentability of the instant invention.

The instant invention requires use of a particular, specific combination of polymers, combined in a particular manner: (1) use of a bioadhesive water insoluble, water swellable cross-linked polycarboxylic polymer, and a water soluble polymer; and (2) combination of these ingredients in a manner that provides progressive hydration of the treating agent upon application to the patient. The particular combination of polymers allows the extended bioadhesion and sustained release provided by the formulation. But even use of this particular combination would not anticipate the claims, unless the product is prepared in a manner that provides progressive hydration. Timpe discloses neither the particular ingredient combination required, nor the requisite method of preparation (or otherwise the resulting progressive hydration).

### **1. Timpe Does Not Provide Progressive Hydration**

First and most importantly, the instant invention requires that the formulation be prepared in a manner that provides progressive hydration. Accordingly, the formulation must be prepared in a manner that provides the treating agent in an initially substantially unhydrated manner -- either by use of a dry method of preparation, or a method that dries the treating agent during processing, so that the formulation ready for use is substantially unhydrated. Progressive hydration is valuable in an extended release formulation, because it enables most of the treating agent to remain dry until much closer to the time that it will be made bioavailable to the patient. Slow hydration over extended time protects treating agents that, for example, may be sensitive to or otherwise degraded or metabolized by moisture, saliva, or pH.

As discussed in the Amendment and Response filed March 6, 2002, pharmaceutical tablets typically are prepared using wet methods, for various reasons including safety and convenience. Such methods would not provide a progressive hydration formulation, because the formulation typically is hydrated during the manufacturing process.

Timpe does not describe particular manufacturing methods for its products, but merely refers to "generally known" procedures, using "common solid or liquid substrates or diluents and adjuvants commonly used in pharmaceutical engineering." See, for example, column 4 at lines 13-18 and 41-45. Thus, Timpe expressly does not seem to contemplate a **special** method that would provide progressive hydration.

Further, Timpe's entire focus is on providing a quick release formulation for quick bioavailability of the treating agent. For example, Timpe stresses "as large a contact area as possible with the mucosa." Column 4, lines 18-22. Timpe's invention focuses primarily on the use of grooves or depressions in the tablet, to further increase the surface area in order to "improve the passage of the active agents contained therein through the mucosa."

Column 2, lines 45-49.

Thus, Timpe's goal is a formulation that practically is the opposite of a progressive hydration formulation, which would make the treating agent bioavailable only slowly, over an extended period of time. Clearly, Timpe would **not** use or teach a progressive hydration formulation. Instead, Timpe's disclosure and teaching actually are inconsistent with, and teach away from, use of the instant invention.

## **2. Timpe Does Not Teach The Claimed Formulation**

Second, and as discussed in prior Responses and Amendments, Timpe does not teach or suggest the particular combination of polymers required by the instant claims. Thus, Timpe's disclosure does not teach even the required ingredients of the instant

invention, let alone a combination of those ingredients to provide a progressive hydration product.

As mentioned above, the instant invention requires use of both a bioadhesive water insoluble, water swellable cross-linked polycarboxylic polymer, and a water soluble polymer. This particular combination of polymers provides extended bioadhesion and sustained release of a treating agent -- whether or not it is manufactured in a progressive hydration product. But without a manufacturing process intended to allow progressive hydration, the treating agent would not be substantially protected from moisture.

The Examiner cites Timpe at column 3, lines 3-9 and 37-43, for the proposition that Timpe teaches a combination of the same polymers. However, in context, Timpe really does not teach or disclose this particular combination at all.

The cited portions of Timpe merely suggest that the bioadhesive tablet should use a substance that develops adhesion when in contact with the mucosa:

The bioadhesive adjuvant should preferably be a substance that develops adhesion when coming into contact with the mucosa, such as a cellulose, a cellulose derivative, a carboxyvinyl polymer, a derivative of a carboxyvinyl polymer, a lectin or natural material or mixtures of said substances.

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A preferred method according to the invention for producing bioadhesive tablets is characterized in that the bioadhesive adjuvant is a substance that develops adhesion when it comes into contact with the mucosa, such as a cellulose, a cellulose derivative, a carboxyvinyl polymer, a derivative of a carboxyvinyl polymer, a lectin or natural material or mixtures of said substances.

Column 3, lines 3-9 and 37-43.

The most that can be said about this disclosure is that "mixtures of said substances" may be used. However, most of the suggested examples are not water soluble polymers or bioadhesive water insoluble, water swellable cross-linked polycarboxylic polymers. And

none of the specific exemplary embodiments included in the disclosure uses a bioadhesive water insoluble, water swellable cross-linked polycarboxylic polymer at all, let alone in combination with a water soluble polymer.

The particular combination of polymers in the instant invention is crucial. Timpe does not in any manner teach, suggest, or disclose this particular combination at all, let alone in a manner that provides progressive hydration. Thus, there clearly is no reasonable basis to conclude that Timpe's disclosure of a list of bioadhesive adjuvants teaches **any** use specifically of at least one water soluble polymer along with at least one bioadhesive water insoluble, water swellable cross-linked polycarboxylic polymer -- let alone in a progressive hydration formulation.

### **THE OBJECTION -- NEW MATTER UNDER 35 U.S.C. § 132**

The amendments to the specification filed November 4, 2002 and March 6, 2002 (apparently referred to jointly in the Office Action as having been filed November 28, 2002) is objected to under 35 U.S.C. § 132 as introducing new matter into the disclosure. The new matter described as not being supported by the original disclosure are: "(1) the time it takes for a tablet to hydrate is decreased; (2) low levels of lactose and corn starch are probably best suited to buccal administration where 12 hours of delivery is usually sufficient; (3) better suited for vaginal administration where release is often required over a period of days; (4) inventors have discovered that by progressively increasing the amount of lactose and corn starch and progressively decreasing the amount of carbomer 974P."

Applicants respectfully disagree. In fact, these very same amendments to the specification were submitted and accepted by the same Examiner in the related U.S. application that issued as U.S. Patent No. 6,624,200, at column 13, lines 19-30, and column 8, lines 41-44; see also column 5, lines 48-56.

As discussed with the Examiner in that related application, these corrections to the specification all involve correction of parts of the specification that interpret the laboratory results reported in the specification in the charts and tables. In fact, these corrections were first raised by an Examiner in one of the foreign related applications, because the original descriptions are not consistent with the results reported in the tables and charts. Thus, clearly one of ordinary skill in the art would recognize (1) that these errors were in the description of the original specification, and (2) the corrections are accurate and necessary to reflect the results of the tables and charts.

Specifically, these corrections are all related to each other, and are based on a single concept. The original text interpreted the tables and charts to conclude that decreasing the proportion of carbomer 974P (the water soluble polymer), while increasing the amount of lactose and corn starch (in order to keep the tablet size constant), surprisingly would allow the formulation to hydrate more rapidly. Reference to the tables and charts demonstrates that this conclusion is backwards -- decreasing the proportion of water soluble polymer instead decreases the rate of hydration of the formulation. The amendments are meant to correct these statements, and are clearly warranted and supported by the original data in the tables and charts.<sup>1</sup>

Table 1 shows nine different tablet formulations, with sequentially decreasing amounts of the water soluble polymer, carbomer 974P. Looking, for example, at formulations 5 and 6, the amount of carbomer 974P is higher in formulation 5 than in formulation 6, while the corn starch and lactose quantities are lower (in order to keep the total tablet weight constant). Formulation 5 is batch number 0029904, which is the subject

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<sup>1</sup> Similarly, the Amendment dated November 4, 2002 also corrected another error that was not raised in the recent Office Action, but that is clearly warranted by the charts and tables. Table 1 lists "carbomer 974P" as an ingredient. The specification was amended to correct the original "934P" to instead read --974P--.

of Table 4, and formulation 6 is batch number 0019904, and the subject of Table 5. See page 17 of the specification, at lines 15-18. Reference to Tables 4 and 5 demonstrate that more testosterone dissolved out of the tablet, at every measuring point past the first hour, for Formulation 5. Thus, the formulation with the higher proportion of carbomer 974P, and the lower proportion of corn starch and lactose, hydrated more quickly. Accordingly, the correct conclusion is that increasing the proportion of carbomer 974P increases the rate of hydration, or decreases the time it takes to hydrate.

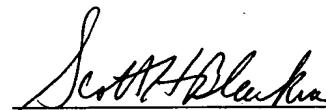
Similarly, the statements regarding suitability for buccal administration or vaginal administration depend on this first conclusion. As mentioned in the specification as filed, 12 hours of delivery is usually sufficient for buccal administration, while vaginal administration is often required over a period of days. Accordingly, formulations with quicker hydration -- and thus less duration -- would be more suitable for buccal administration, while formulations with slower hydration, and longer duration, would be more suitable for vaginal delivery. The amendments correct the conclusion to reflect that less carbomer 974P (and more corn starch and lactose), which yield slower hydration and longer duration, are more suitable for vaginal administration, typically desired over a longer period of time. And then, of course, formulations with the reverse -- more carbomer 974P and less corn starch and lactose -- are more suitable for delivery when a shorter period of time is acceptable, such as buccal delivery.

**CONCLUSION**

In light of these remarks, Applicants respectfully request reconsideration and withdrawal of all rejections, and allowance of all claims. Should there be any remaining issues or rejections, Applicants' representative is available for any questions at the telephone number listed below, assuming that may be convenient for the Examiner.

Please charge the one-month extension fee, and any other fees that may be required with this filing, to Winston & Strawn LLP Deposit Account No. 50-1814.

Respectfully submitted,



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